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Organocatalyzed Enantioselective Direct Mannich Reaction of α-Styrylacetates

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Supporting Information

ABSTRACT: An organocatalyzed direct Mannich reaction of unactivated α-styrylacetates was realized for the first time. By using a quinidine-derived C6′-urea catalyst, the direct Mannich reaction of α-styrylacetates and *N*-tosylimines gave the desired β-amino esters in high yields, diastereoselectivities, and ee values. The reaction provides a highly stereoselective (up to 96:4 dr and 97% ee) and the most straightforward synthesis of functionalized *N*-tosylated β-amino esters. The products can be used as precursors for the highly selective synthesis of tetrahydrofuran derivatives.

Biologically active chiral molecules containing an ester moiety are widespread in nature.[1] Among these ester derivatives, chiral β-amino acid derivatives found among numerous natural products frequently exhibit significant biological activities,[2] and some of them, such as Taxol,[3] have become very important chemotherapeutics. Conceivably, the most straightforward strategy toward the asymmetric synthesis of esters with chiral backbones, such as β-amino esters, would entail the use of unactivated esters directly as the starting materials in a catalytic enantioselective C−C bond formation reaction. Nonetheless, unactivated esters have been widely acknowledged as poor pronucleophiles in asymmetric C−C bond formation reactions because the low acidity of their α-protons and the low electrophilicity of the carbonyl group. To activate the esters for C−C bond formation reactions, traditional methods require the use of a strong base, such as lithium reagents,[4] to generate the enolate form of esters. Unfortunately, developing a catalytic asymmetric version of these reactions on the basis of these approaches proved very challenging.[5] To obviate the problem, various ester surrogates have been developed in the past decades for the synthesis of the desired ester products through asymmetric metal- or organocatalysis.[6,7] Wennemers and co-workers have used activated monothiomalonates in the organocatalyzed synthesis of β-amino thioesters.[7o,p] However, to obtain the corresponding β-amino esters, several synthetic maneuvers are necessary.[7o] The direct use of unactivated esters in catalytic enantioselective C−C bond formation reactions, which can provide a straightforward access to β-amino esters, still remains a challenge in organic chemistry,[5,8] and to our knowledge, simple esters have never been applied in any organocatalytic enantioselective C−C bond formation reactions as pronucleophiles.

On the other hand, from the fundamental aspect of organocatalysis, the reaction of unactivated esters also serves a crucial criterion for determining the scope of the tertiary amine-based organocatalysts. It was postulated that this type of organocatalysts have a functional pK_a barrier for nucleophile activation that lies between the pK_a value of 16 and 17.[9] Indeed,

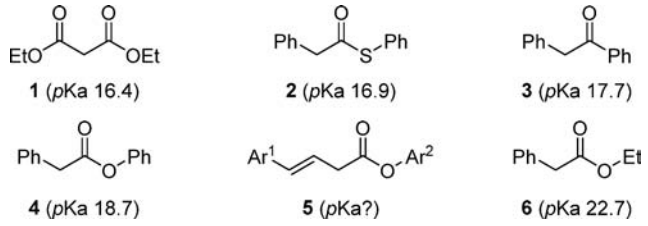

Figure 1. pK_a values of the α-protons of some pronucleophiles in DMSO.[10]

diethyl malonate **1** (Figure 1) with a pK_a of 16.4[10a] has been extensively applied as a pronucleophile in the tertiary amine-catalyzed reactions,[11] whereas phenylthioester **2** with a pK_a of 16.9[10b] proved to be a difficult substrate for this type of reaction.[12] Nonetheless, we recently successfully demonstrated that 9-*O*-protected cinchona alkaloid C6′-(thio)ureas,[13] such as **7a** and **7c** (Figure 2), are effective catalysts for the direct Mannich reaction of phenylthioesters, such as **2**,[14a] and 2-phenylacetophenones, such as **3** (pK_a 17.7[10c]).[14b,c] These studies enhanced the functional pK_a barrier of the tertiary amine-based organocatalysts to a pK_a value of 17.7 for the direct Mannich reactions. In order to continue exploring the upper limit of the pK_a barrier of the tertiary amine catalysts in this reaction, we recently investigated the direct Mannich reactions of phenyl 2-phenylacetate (**4**), which has a reported pK_a value of 18.7,[10b] and aryl (*E*)-4-arylbut-3-enoates (**5**), which should have a pK_a value similar to that of **4** (Figure 1). Herein we wish to report the first direct Mannich reaction[15] of aryl (*E*)-4-arylbut-3-enoates (α-styrylacetates) catalyzed by cinchona alkaloid C6′-(thio)urea catalysts for the highly stereoselective synthesis of *N*-tosylated β-amino esters.

On the basis of our previous studies,[14] we first studied the reaction phenyl 2-phenylacetate (**4**) and *N*-tosylimine **8a** using

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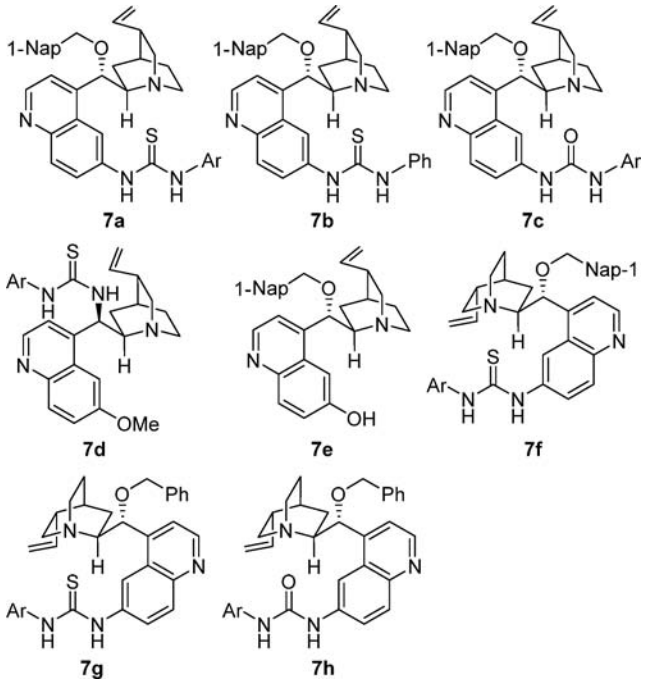
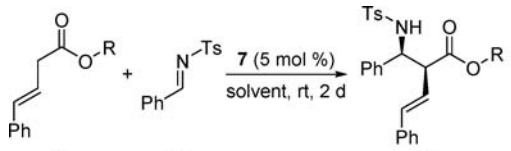


Figure 2. Catalysts used in this study [Nap = naphthyl; Ar = 3,5-$(CF_3)_2C_6H_3$-].

the quinidine-derived C6′-thiourea catalyst **7a** (Figure 2); however, no desired Mannich product could be obtained even after 5 d of reaction at rt. We next screened phenyl (*E*)-4-phenylbut-3-enoate (**5a**) under similar conditions. To our pleasure, the desired Mannich product **9a** was obtained. This reaction provides a straightforward synthesis of chiral *β*-amino ester derivatives. We then further optimized the reaction parameters, and the results are summarized in Table 1. As the results in Table 1 show, the aryl ester group has a major influence on the outcome of this reaction. While the phenyl ester **5a** leads to lower dr and ee values of the product (Table 1, entry 1), the more sterically demanding 2,6-dimethylphenyl ester **5b** gives much improved stereoselectivities (Table 1, entry 2). Unfortunately, this group also makes the substrate less reactive and only a 30% yield of the product **9b** was obtained. An improved yield and ee value were obtained when the ester group was changed to the 1-naphthyl group (**5c**) (Table 1, entry 3), but the product dr remained low. The best compromise was achieved for the 2-methyl-1-naphthyl group (**5d**), which gives a 70% yield of the product **9d** with 81:19 dr and 82% ee (Table 1, entry 4). Using this substrate we then screened some common cinchona alkaloid catalysts (Figure 2). A much lower yield and ee value of **9d** were obtained when catalyst **7b**, which has a phenyl group on the thiourea moiety, was used (Table 1, entry 5). These results hint that the acidity of the thiourea moiety is crucial for both the reactivity and stereoselectivity. When a C6′-urea catalyst **7c** was applied, both the yield and stereoselectivities of the reaction were improved (85:15 dr, 90% ee) (Table 1, entry 6). In contrast, both the C9-thiourea catalyst **7d** and the C6′-hydroxy catalyst **7e** gave very poor results, and the opposite enantiomeric product was obtained, although they have the same quinidine backbone as **7a**–**c** (Table 1, entries 7 and 8). These data suggest that the (thio)urea group and its location are both essential for this reaction. When quinine-derived C6′-thiourea **7f**, which is the pseudoenantiomer of **7a**, was employed, the expected ***ent*-9d** was obtained, but only with 51% ee (Table 1, entry 9). Instead, better ee values of ***ent*-9d** may be obtained with the 9-*O*-benzyl-protected thiourea **7g** and urea **7h** (Table 1, entries 10 and 11), with **7h** giving the yield, dr, and ee value of ***ent*-9d** that almost mirror those obtained with **7c** for **9d** (Table 1, entry 6). The screen of different solvents (Table 1, entries 12–15) with the best catalyst **7c** revealed that toluene (Table 1, entry 6) is the best solvent for this reaction. The attempt to conduct the reaction at 5 °C only led to a lower yield of the product, without any improvement in the product stereoselectivities (Table 1, entry 16).

Table 1. Optimization of the Reaction Parameters for the Direct Mannich Reaction of Aryl (*E*)-4-Phenylbut-3-enoates[a]



entry	cat.	solvent	5/9	yield (%)[b]	dr[c]	ee (%)[d]
1	**7a**	toluene	**a**	61	70:30	58
2	**7a**	toluene	**b**	30	85:15	84
3	**7a**	toluene	**c**	95	72:28	72
4	**7a**	toluene	**d**	70	81:19	82
5	**7b**	toluene	**d**	14	75:25	64
6	**7c**	toluene	**d**	85	85:15	90
7	**7d**	toluene	**d**	45	73:27	45[e]
8	**7e**	toluene	**d**	47	71:29	12[e]
9	**7f**	toluene	**d**	51	86:14	51[e]
10	**7g**	toluene	**d**	52	83:17	86[e]
11	**7h**	toluene	**d**	80	84:16	89[e]
12	**7c**	xylene	**d**	71	87:13	89
13	**7c**	Et_2O	**d**	80	85:15	83
14	**7c**	CH_2Cl_2	**d**	59	84:16	84
15	**7c**	THF	**d**	25	67:33	57
16[f]	**7c**	toluene	**d**	53	85:15	90

[a]Unless otherwise indicated, all reactions were performed with **8a** (0.10 mmol), **5** (0.20 mmol), and catalyst **7** (0.0050 mmol, 5 mol %) in the specified solvent (0.5 mL) at rt. 1-Nap = 1-naphthyl. [b]Combined yield of both diastereomers after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis using a ChiralPak IC column. [e]The opposite enantiomer was obtained as the major product. [f]The reaction was carried out at 5 °C.

Once the reaction parameters were optimized, the scope of this reaction was established by studying different imine and *α*-styrylacetate substrates. The results are collected in Table 2. First, with the *α*-styrylacetate **5d**, we screened several *N*-tosylimines **8**. As the results in Table 2 show, the substituent on the *para*-position of the benzene ring of the imine exerts some influence on the product yields and ee values, but this influence cannot be easily rationalized by the electronic nature of these substituents (Table 2, entries 1–7). On the other hand, except for the trifluoromethyl group (Table 2, entry 7), these substituents have only minimal influence on the diastereoselectivity. The best results were obtained with the 4-CF_3-substituted imine (dr 96:4 and ee 97%) (Table 2, entry 7). The position of the substituent on the benzene ring of the styrylacetates has a more significant influence on the product

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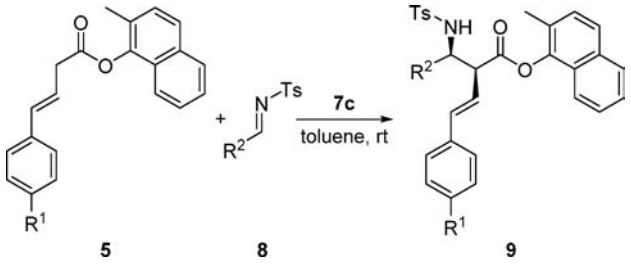
Table 2. Substrate Scope of the Direct Ester Mannich Reaction[a]



entry	R^1	R^2	9 (yield) (%)[b]	dr[c]	ee[d] (%)
1	H	Ph	**d** (85)	85:15	90
2[e]	H	4-MeC_6H_4	**e** (67)	86:14	87
3[e]	H	4-$MeOC_6H_4$	**f** (75)	87:13	94
4	H	4-FC_6H_4	**g** (79)	88:12	86
5	H	4-ClC_6H_4	**h** (80)	84:16	83
6	H	4-BrC_6H_4	**i** (81)	85:15	82
7	H	4-$CF_3C_6H_4$	**j** (83)	96:4	97
8[e]	H	2-ClC_6H_4	**k** (65)	80:20	78
9[e]	H	3-$MeOC_6H_4$	**l** (71)	84:16	86
10[e]	H	(*E*)-PhCH=CH	**m** (72)	80:20	76
11[e]	4-Me	Ph	**n** (73)	83:17	73
12[e]	4-MeO	Ph	**o** (84)	89:11	86
13	4-F	Ph	**p** (80)	95:5	92
14	4-Cl	Ph	**q** (84)	92:8	90
15	4-Br	Ph	**r** (83)	87:13	96
16	3-Cl	Ph	**s** (82)	94:6	92

[a]Unless otherwise indicated, all reactions were performed with **8** (0.10 mmol), **5** (0.20 mmol), and catalyst **7c** (0.0050 mmol, 5 mol %) in toluene (0.5 mL) at rt for 2 days. [b]Combined yield of both diastereomers after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis using ChiralPak IB, IC, or ID columns. [e]The reaction time was 3 days.

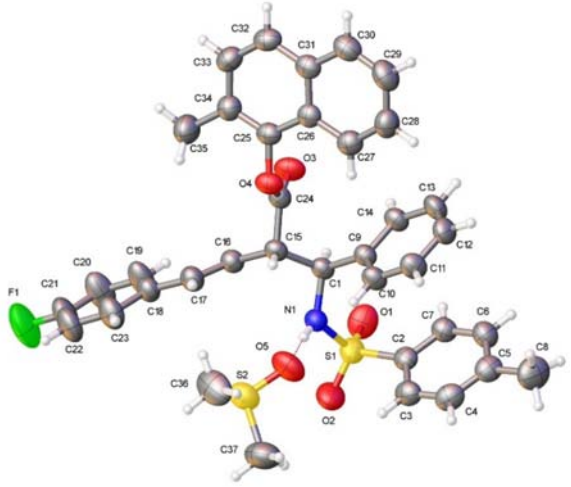
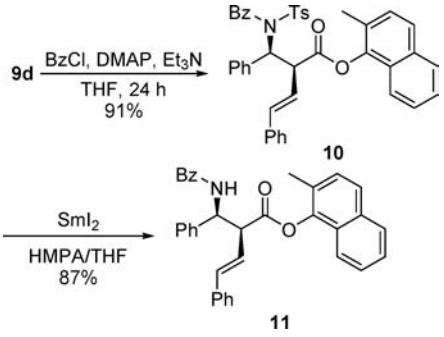


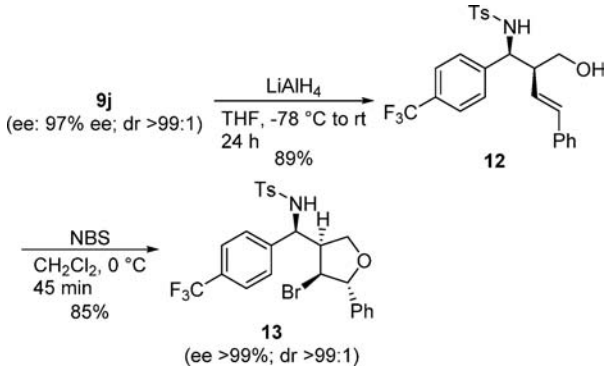
Figure 3. ORTEP drawing of **9p**.

ee values (entries 8 and 9), with 2-chloro-substituted imine giving the lowest ee value (78% ee) (Table 2, entry 8), probably due to steric factors. A cinnamaldehyde-derived tosylimine also participates in this reaction, and the product was obtained in 72% yield, 80:20 dr, and 76% ee (Table 2, entry 10). Nonetheless, aliphatic imines do not yield the desired products, most likely due to the instability of these imines.

Scheme 1. Removal of the Tosyl Group in the Product



Scheme 2. Derivatization of the Reaction Product



Next, using the imine **8a**, we evaluated a few α-styrylacetates. As the results show, the substituent on the *para*-position of the benzene ring had some influence on the stereoselectivities of this reaction (Table 2, entries 11−15), with electron-withdrawing groups (Table 2, entries 13−15) yielding higher product ee values than electron-donating groups (Table 2, entries 11 and 12). Excellent results were also obtained for the 3-chloro-substituted α-styrylacetate (Table 2, entry 16).

The absolute stereochemistry of the reaction product was determined by the X-ray crystallographic analysis of crystals of compound **9p** (Figure 3).[16] On the basis of the X-ray data, the product has a *syn*-stereochemistry with an *S*-configuration for both stereogenic centers.[16] Such a stereochemical outcome is in agreement with those of the Mannich products obtained from phenylthioesters **2** and 2-phenylacetophenones **3** with catalyst **7c** or **7a**,[14] which suggests a similar mechanism for all these reactions.

After protecting the tosylamide group in the Mannich product with a benzoyl group,[17] the tosyl group can be easily removed through a reduction by SmI_2 (Scheme 1).

The highly functionalized β-amino esters obtained in this study should be very useful in organic synthesis. For example, compound **9j** can be conveniently converted to a highly functionalized tetrahydrofuran derivative **13** in a high yield as a single diastereomer with complete retention of the stereochemistry of the original stereogenic centers via a reduction of the ester group and a bromoetherification of the resulting homoallylic alcohol (Scheme 2).[18] Functionalized tetrahydrofurans are very important from both synthetic and medicinal chemistry points of view.[19]

In summary, we have demonstrated that aryl α-styrylacetates can be efficiently activated by cinchona alkaloid-derived C6′-(thio)urea catalysts. Using a quinidine-derived C6′-urea catalyst, the direct Mannich products of *N*-tosyl imines and

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aryl α-styrylacetates were obtained in high yields and excellent diastereo- and enantioselectivities. The reaction provides the most straightforward synthesis of optically enriched *N*-tosylated β-amino esters, which can be used for the stereoselective synthesis of highly functionalized tetrahydrofuran derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01087.

Detailed experimental procedures; ORTEP drawing of compound **9p**; compound characterization data; copy of ^{1}H and ^{13}C NMR spectra and HPLC chromatograms (PDF)

X-ray crystallographic data of compound **9p** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC Deposition No. 1408220 contains the supplementary crystallographic data for **10p**. These data can be obtained free of charge from the Cambridge Crystallographic Data center via www.ccdc.cam.ac.uk/data_request/cif.

(17) The corresponding Boc-protected product did not survive in the tosyl-removal step.

(18) The relative stereochemistry of the two newly formed stereogenic centers in **13** was determined by an NOE experiment together with the reaction mechanism.

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